European Heart Journal Supplements (2008) **10** (Supplement E), E2–E3
doi:10.1093/eurheartj/sun017

EUROPEAN SOCIETY OF CARDIOLOGY®

Editorial

Hot topics in aortic stenosis

Proceedings of a satellite symposium organized by the Scientific Committee of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Study in conjunction with the European Association of Echocardiography of the European Society of Cardiology, which was held during the meeting of the European Association of Echocardiography, EUROECHO, Lisbon, 6 December 2007

Christa Gohlke-Bärwolf[1]* and Jose Luis Zamorano[2]

[1]*Bad Krozingen, Germany and* [2]*Madrid, Spain*

Introduction

This supplement of the *European Heart Journal* addresses important topics in aortic stenosis (AS), based on the presentations made at a satellite symposium of the annual congress EUROECHO 2007 in Lisbon.

Since the first descriptions of acquired calcific AS by Stokes in 1845 and by Mönckeberg in 1904, this disease has undergone a dramatic increase in incidence.

It is the third most common cardiovascular disease after hypertension and CAD and the most common native valve lesion, being present in 43% of all patients with valvular heart disease in the Euro Heart Survey on Valvular Heart disease.[1] Aortic stenosis is also the most common cause for aortic valve replacement, accounting yearly for about 40 000 valve operations in Europe and 95 000 in the United States.

Average life expectancy in the countries of the European Union rose almost 9 years from 1960 to 2000 and continues to increase by 3 months every year, thus the prevalence of AS will increase further, raising important medical and economic issues.

The first epidemiologic study evaluating the prevalence of AS in an unselected elderly population in Finland by two-dimensional and Doppler echocardiography has shown critical native valve stenosis (aortic valve area, $\leq$0.8 cm^2; velocity ratio, $\leq$0.35) in 2.9% of patients over the age of 75 years. Mild calcification of the valve was present in 40% and severe calcification in 13%.[2]

Comparable prevalences were found in Switzerland[3] and in the United States,[4] indicating that AS is a worldwide problem in industrialized countries and constitutes a significant health problem, particularly in the elderly.

Most patients with significant AS progress after an asymptomatic period to a symptomatic state with angina pectoris, heart failure, and sudden death being the classical triad.

The incidence of progression from aortic valve sclerosis as the early lesion to significant valve stenosis ranges between 16% over an 8-year follow-up[5] to 33% over a 5-year follow-up.[6]

Valve surgery is the treatment of choice for symptomatic patients with severe AS. Yet, a considerable number of these patients do not undergo surgery for reasons not well known.[7] So far, there is no recognized or approved medical treatment available. Thus, there is a large and increasing population of patients with progressive degrees of AS requiring therapy.

Recent advances in the elucidation of pathophysiology indicate that calcific AS is an active disease process that shares the common risk factors and characteristics with vascular atherosclerosis. Many experimental studies have shown that hypercholesterolaemia, particularly

* Corresponding author. *E-mail address:* christa-gohlke@t-online.de

oxidized LDL induces inflammatory responses similar to the vascular atherosclerotic processes.

Therefore, a hypothesis was developed, under which AS may be a preventable disease or at least may be amenable to retardation of its progression by medical interventions.

Recently Weiss *et al.*[8] described for the first time the spontaneous occurrence of AS in old LDL receptor knockout mice with moderate levels of LDL cholesterol. Thirty-three per cent of $LDLr^{-/-}$ $ApoB^{100/100}$ mice developed the clinical syndrome of severe AS with high gradients, left ventricular hypertrophy, left ventricular dysfunction, and calcification in the aortic valve. Furthermore, superoxide was present in the aortic valve tissue of these mice indicating oxidative stress. Patients with familial hypercholesterolaemia, with very high LDL cholesterol levels suffer early manifestations of severe coronary disease and AS.

Epidemiological studies have shown that elevated cholesterol levels, hypertension, male sex, smoking, and diabetes—the classical risk factors for atherosclerosis—are also associated with AS.

Thus, there is a large body of evidence from experimental and non-randomized clinical studies indicating the potential for medical prevention or retardation of AS.

In the present issue of the *European Heart Journal Supplement*, a panel of experts presents a comprehensive overview of various aspects of calcific AS, including an update of the pathophysiology, definitions of disease severity, left ventricular structure in different types of pressure overload, systolic left ventricular performance, the present clinical evidence for medical treatment of AS, and a description of the rationale and study design of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study.

N. Rajamannan reviews the latest developments in the pathophysiology of calcific AS, including the role of oxidative stress, inflammatory signalling pathways, angiogenesis, and genetics; the LDL-receptor-related protein-5 signalling pathway and bone morphogenic protein in mediating calcification and stenosis.

N. Jander discusses a specific group of patients with 'severe' AS, as defined by aortic valve area <1 cm^2 with preserved ejection fraction who demonstrate low gradients. He analyses the consistency of recommended parameters for definitions of 'severe' AS in a large patient population and identifies a subgroup with low stroke volume as a possible cause for the low gradient.

E. Gerdts analyses left ventricular structure in different types of pressure overload, including LV geometry and remodelling. Important prognostic implications of LV mass and relative wall thickness in patients with hypertension are presented as well as the results from a comparative study of LV geometric responses in patients from the Losartan Intervention for Endpoint Reduction (LIFE) study and patients with AS.

K. Wachtell discusses systolic LV performance in asymptomatic patients with AS and prognostic implications of impaired LV function. The pathophysiology of LV outflow obstruction is analysed, regarding the question of whether LV hypertrophy is a compensatory or a maladaptive response. The correlation between myocardial contractility and aortic valve area index in asymptomatic patients with mild to moderate AS from the SEAS study is presented as well as gender differences in AS.

T. R. Pedersen reviews the current clinical evidence for the hypothesis that statin treatment may retard progression of AS and influence clinical endpoints—such as morbidity, mortality and the need for surgical valve replacement. The completed and ongoing studies with various lipid-lowering drugs are discussed. If the hypothesis can be proven, there might be a chance for prevention of progression from pre-stenotic aortic sclerosis to symptomatic severe AS, thereby reducing the burden of this disease and improving the prognosis of these patients.

Funding

The symposium and these proceedings were supported by an educational grant from Merck/Schering-Plough.

References

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. *Eur Heart J* 2003;**24**:1231–1243.
2. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993;**21**:1220–1225.
3. Lorz W, Cottier C, Gyr N. The prevalence of aortic stenosis in an elderly population: an echocardiogaphic study in a small Swiss community; Cardiology in the Elderly 1993;**1**:511–515.
4. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease: Cardiovascular health study. *J Am Coll Cardiol* 1997; **29**:630–634.
5. Cosmi JE, Kort S, Tunick PA, Rosenzweig BP, Freedberg RS, Katz ES, Applebaum RM, Kronzon I. The risk of the development of aortic stenosis in patients with benign aortic valve thickening. *Arch Intern Med* 2002;**162**:2345–2347.
6. Faggiano P, Antonini-Canterin F, Erlicher A, Romeo C, Cervesato E, Pavan D, Piazza R, Huang G, Nicolosi GL. Progression of aortic valve sclerosis to aortic stenosis. *Am J Cardiol* 2003;**91**:99–101.
7. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Bärwolf C, Boersma E, Ravaud P, Vahanian A. Decision making in elderly patients with severe aortic stenosis: Why are so many denied surgery? *Eur Heart J* 2005;**26**:2714–2720.
8. Weiss RM, Ohashi M, Miller JD, Young SG, Heistad DD. Calcific aortic valve stenosis in old hypercholesterolemic mice Circulation 2006; **114**:2065–2069.